FORM PTO-1390 (REV. 11-2000) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
0933-0181P	
U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	
10/069763 NEW	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FI00/00733	August 30, 2000	August 31, 1999

TITLE OF INVENTION
METHOD FOR IDENTIFYING AN INDIVIDUAL AT RISK FOR VASCULAR AND CANCER DISEASE

APPLICANT(S) FOR DO/EO/US
SIPPONEN, Pentti; HARKONEN, Matti; SUOVANIEMI, Osmo

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau). WO 01/16356
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is transmitted herewith.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4)
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☒ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 20. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98, Form PTO-1449(s), and International Search Report (PCT/ISA/210) with 4 cited document(s).
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information:
    1.) Form PCT/IB/304
    2.) Form PCT/IB/308
    3.) International Preliminary Examination Report (PCT/IPEA/409)
    4.) Zero (0) Sheets of Formal Drawings

JC19 Rec'd PCT/PTO 28 FEB 2002

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
10/069763 NEW	PCT/FI00/00733	0933-0181P

21. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1,040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO. **$740.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4). **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$ 1,040.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	**$ 0.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	6 - 20 =	0	X **$18.00**	**$**	**0.00**
Independent Claims	1 - 3 =	0	X **$84.00**	**$**	**0.00**
MULTIPLE DEPENDENT CLAIM(S) (if applicable)		Yes	+ **$280.00**	**$**	**280.00**
			TOTAL OF ABOVE CALCULATIONS =	**$**	**1,320.00**
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				**$**	**0.00**
			SUBTOTAL =	**$**	**1,320.00**
Processing fee of **$130.00** for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)).			+	**$**	**0.00**
			TOTAL NATIONAL FEE =	**$**	**1,320.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property			+	**$**	**40.00**
			TOTAL FEES ENCLOSED =	**$**	**1,360.00**
				Amount to be: refunded	**$**
				charged	**$**

a. ☒ A check in the amount of $ **1,360.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account. No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2448.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to:
Birch, Stewart, Kolasch & Birch, LLP or Customer No. 2292
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Date: February 28, 2002

By _____ #34,868
for Gerald M. Murphy, Jr., #28,977

/rem

PATENT
0933-0181P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	SIPPONEN, Pentti et al.		
Int'l. Appl. No.:	PCT/FI00/00733		
Appl. No.:	New	Group:	
Filed:	February 28, 2002	Examiner:	
For:	METHOD FOR IDENTIFYING AN INDIVIDUAL AT RISK FOR VASCULAR AND CANCER DISEASE		

PRELIMINARY AMENDMENT

BOX PATENT APPLICATION
Assistant Commissioner for Patents
Washington, DC 20231

February 28, 2002

Sir:

The following Preliminary Amendments and Remarks are respectfully submitted in connection with the above-identified application.

AMENDMENTS

IN THE SPECIFICATION:

Please amend the specification as follows:

Before line 1, insert --This application is the national phase under 35 U.S.C. § 371 of PCT International Application No. PCT/FI00/00733 which has an International filing date of August 30, 2000, which designated the United States of America.--

Docket No. 0933-0181P

REMARKS

The specification has been amended to provide a cross-reference to the previously filed International Application.

Entry of the above amendments is earnestly solicited. An early and favorable first action on the merits is earnestly solicited.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By #37,868
for Gerald M. Murphy, Jr., #28,977

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GMM/rem
0933-0181P

METHOD FOR IDENTIFYING AN INDIVIDUAL AT RISK FOR VASCULAR AND CANCER DISEASE

Field of the invention

The present invention relates to a combination diagnostic method for identifying individuals who are at risk for coronary and vascular, as well as cancer diseases.

The method according to the invention is based on the combination of two tests carried out on a blood or serum sample in order to identify individuals prone to develop or exhibiting elevated levels of homocysteine, which individuals are thus at risk of developing afflictions resulting from such elevated levels, such as cardio- and cerebrovascular disease, including atherosclerosis and ischaemic stroke, as well as cancer diseases.

Background of the invention

A number of different gastric diseases or conditions, such as chronic atrophic gastritis, pernicious anaemia, ventricular ulcer, gastric polyposis and the Ménétrier disease (giant hypertrophic gastritis) precede gastric cancer. Clearly identifiable changes of the mucosa are dysplasia and adenoma. It has been established that in almost all diseases the risk is mediated over chronic atrophic gastritis.

Chronic gastritis means a prolonged inflammatory condition of the gastric mucosa. The disease can coarsely be divided into the superficial and the atrophic form. In superficial gastritis, the inflammatory cell infiltration is concentrated below the surface epithelium. In case the inflammation progresses and diffuses between the specific gastric secretory glands, one refers to chronic atrophic gastritis. In such a case, the normal glandular structures of the gastric mucosa are at least partly substituted by metaplastic changes.

The relative risk of gastric cancer in patients suffering from atrophic gastritis in the corpus area of the stomach has been estimated, as calculated from the Finnish cancer statistics, to be about 4- to 5-fold as compared to persons having a healthy mucosa. In addition, there is a risk for falling ill with pernicious anaemia due to intrinsic factor deficiency and B12 vitamin absorption disturbance. In severe atrophy of the antrum area, the risk is even 18-fold. If atrophic changes appear both in the antrum and the corpus area (pangastritis), the risk can increase to even 90-fold.

The publication WO 96/15456 discloses a method for screening for the risk of gastric cancer according to which atrophy in the mucosa either of the corpus or the antrum area, or of both, is determined by determining the pepsinogen I (PGI) and gastrin-17 (G-17) analyte levels in a serum sample, and comparing the levels so determined to a method-specific cut-off value for respective analyte. The levels determined are preferably also compared to a method-specific reference value for respective analyte.

A serum PGI value below the specific cut-off value for PGI indicates atrophic gastritis in the corpus area of the stomach. If the serum G-17 concentration is below its cut-off value, the atrophy is located in the antrum area of the stomach. In pangastritis, the serum PGI is below the cut-off value and the serum G-17 value is at the lower limit of its reference value.

Methylenetetrahydrofolate reductase (MTHFR) is an intracellular enzyme that is needed for remethylation of homocysteine to methionine. Impaired function of this enzyme is caused by defects in the structure of the MTHFR gene, or by nutritional deficiencies of *i.a.* folate, vitamin B6 and/or vitamin B12. Impaired function of the MTHFR enzyme results in an increase in the serum/plasma level of homocysteine (homocysteinemia) and in homocysteinuria. Increased serum/plasma levels of homocysteine has in many studies shown to be associated with an increased risk for various coronary and vascular diseases, a high serum/plasma level

of homocysteine above the reference value being a serious independent risk factor for coronary and vascular disease and ischaemic stroke.[1-5]

The atherogenic influence of homocysteine is thought to be based on an increased production of reactive oxygen species which enables lipid peroxidation.
The supply of sufficient B12 vitamin is necessary for folate metabolism and normal blood production, as well as for the function of the nerve cells. Vitamin B12 forms a complex with a protein, the intrinsic factor, produced by the mucosa of the corpus area of the stomach, which complex is resorbed in the lower part of the ileum. This is the preferred resorption form of vitamin B12.

A deficiency of intrinsic factor, as a result of atrophic gastritis or stomach cancer, especially in the corpus area of the stomach, will ultimately lead to a deficiency in B12 vitamin in the body and hence to an increase in the homocysteine concentration. It would thus be highly valuable to identify those subjects who have or are at a high risk for vitamin B12 deficiency due to atrophic gastritis, and who therefore might have an elevated serum or plasma level of homocysteine. In those persons an early initiation of vitamin B12 supplementation would be beneficial in the prevention of vascular diseases. It would also be valuable to be able to identify those individuals which would be at risk of cancer due to overproduction of intracellular oxygen radicals, and in whom a B12 vitamin supplementation or other treatment could be beneficial.

Summary of the invention

The present invention is directed to a method for combining an assay of determining, in a serum sample, a marker for atrophic gastritis in combination with an assay for homocysteine, in order to assist in the diagnosis of, or in the determination of the risk of vascular, as well as cancer diseases in an individual, the term vascular being understood broadly to include any coronary or vascular disease which can result from the atherogenic influence of homocysteine.

The method according to the invention is a method for identifying an individual at risk for vascular and cancer disease, the method comprising the steps of

- determining quantitatively the pepsinogen I (PGI) analyte concentrations in a serum sample from said individual,
- selecting a method specific cut-off value for the said analyte,
- comparing the analyte concentration so determined to the method-specific cut-off value for the analyte, and
- determining the homocysteine concentration in a serum sample from the individual, and comparing it to a method-specific reference value for homocysteine.

The present invention thus allows for the identification of an individual having a serum pepsinogen I concentration below the method-spe : cut-off value for serum pepsinogen I and a serum homocysteine concentr : above the reference value for homocysteine, as being an individual with an increased risk of, or having a predisposition for vascular and/or cancer disease.

The determination of the serum PGI and homocysteine concentrations can take place in any order, in order to simultaneously obtain knowledge of both the serum PGI and homocysteine levels for the purpose of assisting in the diagnosis of, or assessing the risk of vascular disease or cancer. However, according to an embodiment of the invention, the serum PGI concentration is determined and compared to its determined or selected method-specific cut-off value, and for further diagnosis an individual is selected who has a serum PGI concentration value below its method-specific cut-off value. In this embodiment, only the individuals which exhibit low serum PGI values indicative of corpus atrophy, are screened for homocysteine.

According to one embodiment of the invention, also the B12 concentration is determined in the serum of the said individual, and compared to a method-specific reference value for vitamin B12.

The invention includes a step of comparing the measured analyte concentrations to method-specific cut-off or reference values for said analytes. The selection of such values is well known to a person skilled in the art, and depends on the specificity and sensitivity chosen for the test method used for the determination of the analyte concentrations, see e.g. William J Marshall, Clinical Chemistry, Third Edition, 1995, Mosby.

Thus according to a preferred embodiment, the present invention is especially aimed at screening such individuals, which still do not exhibit a B12 vitamin deficiency, that is which exhibit substantially normal B12 vitamin levels, but which due to low PGI values are diagnosed for atrophy in the corpus area of the stomach and which also have high homocysteine serum levels. Such an identification makes it possible to already at an early stage resort to preventative measures, for example to B12 supplementation, in order to counteract the development of the afflictions associated with elevated homocysteine levels.

Detailed description of the invention

1. Determination of pepsinogen I (PGI)

The method of determining PGI in a serum sample can be carried out as is described in the publication WO 96/15456, which publication is included herein for reference.

The said method preferably includes the steps of using poly- or monoclonal antibodies to pepsinogen I in an immunological method for the determination of pepsinogen I. Suitably the reaction is carried out on a suitable support, such as a plastic, glass or cellulose support, for example on a microplate. The immunological methods can be carried out in a known manner, using e.g. absorbance, luminescence or fluoresence techniques for measuring the said pepsinogen I concentration in the sample.

If the serum pepsinogen I concentration is below the cut-off value, which depending on the specificity and sensitivity agreed upon for the method in question, is 20-30 μg/l, which corresponds to appr. 450 - 690 pmol/l, there is atrophy in the corpus area of the stomach. The normal or reference value for PGI is in the range of 25 - 120 μg/l.

2. Determination of homocysteine

Homocysteine levels in serum can be determined according to any of the methods known *per se* for this purpose and which are also commercially available, *e.g.* in kit form. The established method for quantifying total homocysteine in plasma or serum is high performance liquid chromatography with radioactive, fluorescent or electrochemical detection. Also an enzyme immunoassay (EIA) method has been developed (Bio-Rad Laboratories; Axis-Shield A/S) as well as a fluorescence polarisation immunoassay (FPIA; Abbott Laboratories), the immunoassay including pretreating the specimens with dithiothreitol and adenosine, followed by an enzymatic step to form S-adenosyl-L-homocysteine, and total homocysteine is measured e.g. using monoclonal anti-S-adenosyl-L-homocysteine antibodies, see *e.g.* US 5,631,127.

The reference values for homocysteine is to some degree method-specific, but generally varies between appr. 5 to 15 μmol/L. A serum homocysteine level which is above the method-specific reference level for homocysteine is taken as constituting a risk factor, as explained above. A homocysteine level of above 15 μmol/L can in most cases be considered to constitute such an elevated level constituting a clear risk factor.

3. Determination of B12-vitamin

According to the invention, the method of diagnosis includes an optional method of determining the B12 vitamin concentration in the serum sample. The B12-vitamin (cobalamin) concentration can be determined according to any of the methods

per se known for this purpose. Such known methods include microbiological assay of serum B12 employing an organism, such as *Euglena gracilis* or *Lactobacillus leichmannii* which requires cobalamin for growth. Also radioisotope dilution assays for B12 vitamin have been utilized and such assay techniques are well documented in the literature, e.g. Lau *et al.*, "Measurement of serum B12 levels using Radioisotope Dilution and Coated Charcoal", Blood, 26 (1965), 202. Radioisotope dilution methods are more rapid and give results comparable with those of e.g. the *Euglena* assay, provided the binding protein is specific for biologically active cobalamin. A standardized pure or purified intrinsic factor preparation is most satisfactory as the binding protein as it binds specifically to true cobalamin rather than cobalamin analogues.

The radioisotope dilution assay of B12 generally includes the step of freeing endogenous B12 from its natural binding protein e.g by boiling at a selected pH and then adding a measured amount of the radioisotope 57Co-B12, and a limited amount of binding protein. All of the binding protein will be bound by some form of B12 since the amount of radioisotope B12 added is sufficient to bind the small amount of protein. As both the natural and the radioactive B12 compete to bind with the binding protein, the degree to which the radioactive count of the protein bound B12 was inhibited is indicative of the amount of B12 in the sample. This method has been modified by Lau, *supra,* by separating unbound B12 from protein bound B12 by protein coated charcoal and the radioactivity of the supernatant liquid containing the mixture of bound radioactive B12 and bound non-radioactive B12 is counted for radioactivity. The serum B12 concentration is then calculated from the count, often by comparison with a standard chart. Radioassay kits are commercially available for carrying out the method.

B12 vitamin deficiency has also been determined using e.g. chemiluminiscence receptor assays (Wentworth, S. *et al.*, Clin. Chem., vol 40 537-540), radioimmunoassays (Endres, D.B., *et. al.* Clin. Chem., Vol. 24, 460-465) as well as nonisotopic binding assays, CEDIA, cloned enzyme donor immunoassays (van der Weide, J. *et al.* Clin. Chem., Vol. 38, 766-768).

The reference value for B12 varies between 200-900 ng/l, corresponding to appr. 170 to 700 pmol/l.

In our recent unpublished work we found that 50% of those subjects suffering from corpus atrophy (SPGI < 25 μg/l) whose vitamin B12 serum concentration was below the lower part of the reference limit (< 170 pmol/l) had markedly increased serum homocysteine concentration (mean 33.3 μmol/l, 16-157 μmol/l). In addition, 22% of those subjects whose vitamin B12 serum concentration was between 180 - 230 pmol/l (reference values 170 - 700 pmol/l) had also an increased homocysteine concentration (mean 18.9 μmol/l, 16 - 25 μmol/l).

The present invention also relates to a kit for use in the method according to the invention the kit comprising

- means for determining the PGI concentration in a serum sample,
- means for determining the concentration of homocysteine in a serum sample.

The kit according to the invention can comprise a combination of the individual components needed to quantitatively determine the serum pepsinogen I and the homocysteine concentration in a blood serum sample. For this purpose the kit can comprise separate vials or containers for the necessary components, such as antibodies and substrates to be used for the determination of the analyte.

References

1. Boushey, C.J., Beresford, S.A.A., Omenn, G.S., Motulsky, A.G., JAMA 1995; 274:1049-57

2. Graham, I.M., Daly, L.E., Rafsum, H.M. *et. al.*, The European Concerted Action Project, JAMA 1997; 277:1775-81

3. Jacobsen, O.W., Clin Chem 1998; 44:1833-43

4. Mogadashian, M. H., McManus, B.M., Frohlich, J.J., Arch Intern Med 1997; 157: 2299-2308

5. Rafsum, H., Ueland, P.M., Nygård, O., Vollset, S.E., Rev Medicine 1998; 49:31-62.

Claims

1. Method for identifying an individual at risk for vascular and cancer disease, the method comprising the steps of

- determining quantitatively the pepsinogen I (PGI) analyte concentrations in a serum sample from said individual,
- selecting a method specific cut-off value for the said analyte,
- comparing the analyte concentration so determined to the method-specific cut-off value for the analyte, and
- determining the homocysteine concentration in a serum sample from the individual, and comparing it to a method-specific reference value for homocysteine, whereby a serum pepsinogen I concentration below its method-specific cut-off value, and a serum homocysteine concentration above its method-specific reference value identifies the individual as an individual with an increased risk of vascular and cancer disease.

2. The method according to claim 1, comprising determining the serum PGI concentration, and selecting for further determination of the homocysteine concentration an individual who exhibits a serum PGI concentration below its cut-off value.

3. The method according to claim 1 or 2, comprising the further step of determining the B12 vitamin concentration in the sample and comparing it to a method-specific reference value.

4. Kit for carrying out the method according to claim 1, comprising
- means for determining the PGI concentration in a serum sample,
- means for determining the homocysteine concentration in a serum sample.

5. The kit according to claim 4 wherein the means for determining the pepsinogen I and homocysteine concentration comprise immunological means.

BIRCH, STEWART, KOLASCH & BIRCH, LLP

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ATTORNEY DOCKET NO.
0933-0181P

PLEASE NOTE: YOU MUST COMPLETE THE FOLLOWING:

COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT AND DESIGN APPLICATIONS

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated next to my name; that I verily believe that I am the original, first and sole inventor (if only one inventor is named below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Insert Title: METHOD FOR IDENTIFYING AN INDIVIDUAL AT RISK FOR VASCULAR AND CANCER DISEASE

the specification of which is attached hereto. If not attached hereto,

Fill in Appropriate Information — For Use Without Specification Attached:

the specification was filed on _____ as
United States Application Number _____ ;
and amended on _____ (if applicable); and/or
the specification was filed on 30 August 2000 as PCT
International Application Number PCT/FI00/00733 ; and was
amended under PCT Article 19 on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months (six months for designs) prior to this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Insert Priority Information: (if appropriate)

Prior Foreign Application(s)			Priority Claimed	
19991836 (Number)	Finland (Country)	08/31/1999 (Month / Day / Year Filed)	☒ Yes	☐ No
_____ (Number)	_____ (Country)	_____ (Month / Day / Year Filed)	☐ Yes	☐ No
_____ (Number)	_____ (Country)	_____ (Month / Day / Year Filed)	☐ Yes	☐ No
_____ (Number)	_____ (Country)	_____ (Month / Day / Year Filed)	☐ Yes	☐ No

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

Insert Provisional Application(s): (if any)

_____ (Application Number) _____ (Filing Date)
_____ (Application Number) _____ (Filing Date)

All Foreign Applications, if any, for any Patent or Inventor's Certificate Filed More than 12 Months (6 Months for Designs) Prior to the Filing Date of This Application:

Insert Requested Information: (if appropriate)

Country	Application Number	Date of Filing (Month / Day / Year)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States and/or PCT application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States and/or PCT application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Insert Prior U.S. Application(s): (if any)

(Application Number)	(Filing Date)	(Status — patented, pending, abandoned)
_____	_____	_____
_____	_____	_____

I hereby appoint the following attorneys to prosecute this application and/or an international application based on this application and to transact all business in the Patent and Trademark Office connected therewith and in connection with the resulting patent based on instructions received from the entity who first sent the application papers to the attorneys identified below, unless the inventor(s) or assignee provides said attorneys with a written notice to the contrary:

Raymond C. Stewart	(Reg. No. 21,066)	Terrell C. Birch	(Reg. No. 19,382)
Joseph A. Kolasch	(Reg. No. 22,463)	James M. Slattery	(Reg. No. 28,380)
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Charles Gorenstein	(Reg. No. 29,271)	Gerald M. Murphy, Jr.	(Reg. No. 28,977)
Leonard R. Svensson	(Reg. No. 30,330)	Terry L. Clark	(Reg. No. 32,644)
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Joe McKinney Muncy	(Reg. No. 32,334)	John A. Castellano	(Reg. No. 35,094)
Donald J. Daley	(Reg. No. 34,313)	John W. Bailey	(Reg. No. 32,881)

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of First or Sole Inventor: Insert Name of Inventor → Insert Date This Document is Signed

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Residence (City, State & Country)	CITIZENSHIP

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* DATE OF SIGNATURE